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Effect of Injury and Infection on Visceral Metabolism and Circulation

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To characterize the role of the liver and kidney in the metabolic response to injury and infection, selective catheterization of the hepatic (42 veins) and renal veins (21 veins) was performed in 31 burn patients (mean burn size: 51% TBS), studied 4–129 days postinjury. Blood flow was determined by standard clearance techniques (ICG and PAH), and simultaneous arterial and hepatic and/or renal vein blood was obtained for oxygen, glucose, lactate, pyruvate, and amino acids. Patients studied in the first to third weeks postinjury were classified as *noninfected* (8 studies), *bacteremic* (8 studies), or *bacteremic with complications* (5 studies). There was no difference in age, weight, mean burn size, pulse rate, blood pressure, rectal temperature, total body oxygen consumption, or cardiac index among these groups. Estimated hepatic blood flow (EHBF) and hepatic substrate balance of these patients were compared with postabsorptive normal subjects in the literature (mean ± SEM or range).

	Normal	*Noninfected*	*Bacteremic*	*Complicated Bacteremic*
Hepatic Blood Flow (l/min·m²)	0.63–0.85	1.54 ± 0.12	1.74 ± 0.17	1.19 ± 0.18
Oxygen Uptake (ml/min m²)	34–40	68 ± 4	66 ± 5	73 ± 3
Glucose Output (μM/min m²)	350–450	635 ± 35	835 ± 54	362 ± 60
Lactate Uptake (μM/min m²)	130–160	377 ± 77	431 ± 107	268 ± 108
Alanine Uptake (μM/min m²)	30–45	124 ± 31	213 ± 40	42 ± 11

Thermal injury alone resulted in marked increases in EHBF, hepatic oxygen uptake, and glucogenesis. The added insult of bacteremia significantly increased hepatic glucose output; as clinical sepsis progressed, glucose output decreased sharply. The kidney consistently demonstrated a net uptake of glucose in all studies. The changes in hepatic glucose output in bacteremic patients occurred without significant differences in EHBF, oxygen utilization or lactate uptake, but were associated with marked alterations in amino acid uptake.

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THE METABOLIC RESPONSE to major injury is characterized by hypermetabolism,[9,34] increased hepatic glucose production,[14,18,36] accelerated ureagenesis, and increased urinary nitrogen excretion.[9,23] Multiple trauma or severe injury is frequently complicated by infection. As the septic process progresses, organ dysfunction occurs resulting in increased morbidity and mortality. To gain further understanding of the metabolic alterations which occur following trauma and trauma complicated by infection, we studied splanchnic and renal blood flow, regional oxygen consumption, and substrate exchange in patients with extensive thermal injury who were free of infection, in burned patients with bacteremia, and in burned patients with sepsis associated with severe organ dysfunction.

Materials and Methods

Subjects

Twenty-nine male and two female burn patients were studied (mean burn size: 51% total body surface, range: 41–83.5%). Patients had no known pre-existing disease prior to injury. While most were studied between the first and third weeks postinjury, some patients were studied as early as the fourth postburn day or as late as 127 days postinjury. Serial measurements were performed on 6 patients to evaluate the effect of time and septic complications on posttraumatic circulation and metabolism. Patients studied between the fourth and twenty-ninth postburn days were matched for burn size and placed into one of three categories defined prior to study and based on clinical and laboratory criteria (Table 1).

Noninfected patients. These patients were: 1) normotensive and hemodynamically stable after an uneventful resuscitation; 2) in a normal state of hydration with hematocrits greater than 30 and without abnormalities in serum osmolality, pH, or concentrations of electro-

TABLE 1. *Characteristics of Patients (Mean ± SEM)*

	Noninfected Burn Patients	Bacteremic Burn Patients	Bacteremic Burn Patients With Complications
Number of Patients	7	8	4
Number of Studies	8	8	5
Age (Years)‡	26 ± 2	26 ± 2	33 ± 3
Weight (kg)	74.5 ± 4.7	67.2 ± 5.5	83.9 ± 4.0
Body Surface Area (m^2)	1.90 ± 0.07	1.81 ± 0.07	2.03 ± 0.06
Per Cent Total Body Surface Burn*	58.0 ± 5.0	62.0 ± 3.0	64.5 ± 4.0
Per Cent 3° Degree Burn*	32.0 ± 6.0	14.0 ± 6.0	22.5 ± 7.5
Post Burn Day Studied	10 ± 1	13 ± 2	15 ± 6
Positive Blood Cultures Before Day of Study	0	6/8	5/5
Positive Blood Cultures on Day of Study	0	8/8†	5/5§
Died	1/7	3/8	4/4

* As determined by the clinical assessment to the closest 0.5%.

† *Staphylococcus aureus* was recovered in four cultures, and gram negative organisms were identified in the remaining (three *Pseudomonas aurogenosa* and one *Enterobacterclocca*).

‡ Age and burn size were considered only once in the description of group characteristics.

§ *Staphylococcus aureus* was recovered in four studies and *Pseudomonas aurogenosa* was found on the other.

These cultures represented similar findings to those observed on the day of study. Approximately half of the cultures grew *Staphylococcus aureus* and the remaining grew gram negative organisms.

lyte, blood urea nitrogen, or creatinine; 3) free of systemic infection prior to and including the day of study, as determined by clinical symptoms and signs, chest x-rays, and urine and blood cultures; and 4) alert, cooperative and able to participate in the study.

Bacteremic patients. The subjects met the first two criteria of the noninfected patients but had signs of infection as characterized by changes in mental status (6/8 patients), ileus (5/8 patients), glucosurea (6/8 patients), and previous blood stream cultures (6/8 patients). All patients in this group had bacteria cultured from their bloodstream at the time of the investigation and were receiving systemic antibiotics. Since they were studied shortly after the onset of infection, however, no clinical or biochemical evidence of specific organ dysfunction or multiorgan failure was present in this group.

Bacteremic patients with complications. Although these patients had apparently been successfully resuscitated, they became septic (as documented by positive bloodstream cultures) early in their posttraumatic course and developed evidence of multiorgan failure. At the time of the study, all had undergone alterations in mentation as characterized by confusion (2/5 patients) or obtundation (3/5 patients), and three required mechanical ventilatory support. Renal impairment, as documented by serum creatinine greater than 1.5 mg/dl, was present in four subjects. All of these subjects maintained adequate circulation and cardiovascular stability for several days before and during the study.†

† One individual required 36 hours of pressor support (dopamine) at the time of the initial septic episode, and a second subject became hypotensive during the onset of sepsis but responded to volume support. Both of these events occurred approximately one week before the subjects were studied.

Subject Preparations

All patients were treated in a similar manner. Patients studied within the first three weeks of injury had not undergone primary wound excision or other operative treatment requiring general anesthesia. Most wounds were treated by the exposure method, using either silver sulfadiazine cream (Silvadine®)‡ or 11% mafenide acetate (Sulfamylon®).§ In a few individuals, small wound areas were covered with dressing soaked with 5% mafenide solution.

Patients received vigorous nutritional support during their hospitalization. Those who could not eat received tube feedings or parenteral nutrition. Nutrient intake for at least three days before each study satisfied at least 80% of the patients' metabolic requirements and at least half of the administered calories were carbohydrate. Body weight was generally stable during the week before the study, and no patient studied within three weeks of injury exhibited a body weight loss exceeding 5% of preinjury weight at the time of initial study.

Study Design

Patients were studied in the early morning after fasting since midnight. Those who required intravenous fluid to maintain a normal state of hydration received 0.04 molar nutrient free sodium chloride infusions for six hours before and throughout the study. While routine clinical care continued in the morning, patient manipulation was minimized for at least six hours be-

‡ Marion Laboratories, Inc., Pharmaceutical Division, 10236 Bunker Ridge Road, Kansas City, MO 64137.

§ Winth op Laboratories, 90 Park Avenue, New York, NY 10016.

fore the study. Patients who were not able to rest during this period of time were not studied.

Subjects were taken to a nearby x-ray suite where a #7 J-catheter was advanced under fluoroscopic control through the femoral vein and inferior vena cava to deep within the right hepatic vein (3–4 cm from the wedge position). In selected patients, the catheter was first directed into the right renal vein and blood samples obtained before proceeding to the hepatic vein. Once proper position was established in the hepatic vein, the catheter was secured in the groin with a silk suture and adhesive tape and the subject moved to an environmental chamber.[35] Chamber temperature was maintained at 30 C and relative humidity between 40 and 50%. Under local anesthesia, an arterial catheter (a #21 polyvinyl tubing) was inserted into the left femoral artery and, if not present, a venous catheter (#18) was inserted into a large peripheral vein. Catheter patency was maintained by slow infusion of 0.04 molar sodium chloride solution (a syringe pump maintained this patency of the arterial catheter while gravity infusion was used for the intravenous lines). Total time required for catheter insertion and initial preparation was 1 to 1.5 hours. Following this period, the subjects were allowed to rest for at least one hour in the semi-dark, warm, quiet room.

After the equilibration period, blood samples were drawn simultaneously from arterial and hepatic venous catheters and subsequently analyzed for oxygen content, whole blood glucose, lactate, and pyruvate, and plasma amino acid concentrations. A bolus injection of indocyanine green dye (ICG: 0.5 mg/kg) was then given via the peripheral venous catheter and simultaneous arterial and hepatic venous blood samples obtained at two, four, six, ten, and 12 minutes postinjection. The rate of plasma ICG clearance over this time period provided a measure of splanchnic or estimated hepatic blood flow.[28]*

Cardiac output was then determined using the standard ICG dye dilution technique.[31] Three to five determinations were performed and an average value obtained. A canopy hood was then placed over the subject's head and oxygen consumption determined by the open circuit technique over the next 15–20 minutes.[3] Oxygen consumption of patients on ventilators was determined by Douglas bag techniques.

Patients usually slept throughout the 1.5- to two-hour study period. At the end of each study, pulse rate, blood pressure, and rectal temperature were obtained. X-ray confirmation of hepatic vein catheter position was routinely performed initially and in selected individuals throughout the study.

Study Methods

Heparinized blood samples were analyzed for oxygen content ($Lex\text{-}O_2\text{-}Con$).¶ Whole blood glucose was measured by the glucose oxidase method,[31] lactate by enzymatic technique,[31] and plasma amino acids by standard chromatography.# Hematocrits were determined on all samples and were within 5% for each matched sample set. All measurements were performed in triplicate, and an average value reported. Indocyanine green dye concentrations were determined using a spectrophotometer (Gilford Model #240), and splanchnic blood flow calculated from the proportionality constant for plasma ICG disappearance, the hepatic ICG extraction ratio, and hematocrit.[28] Extrapolation of the arterial ICG disappearance curve to time zero provided an estimate of plasma volume, which compared favorably with simultaneous I^{131}-albumin plasma volume determinations performed in five individuals. Splanchnic substrate exchange and oxygen consumption were calculated by multiplying splanchnic blood flow by arterial–hepatic venous concentration differences.

Paired and unpaired t-tests were used when appropriate and significance was considered at the $p < 0.05$ level. When comparing the three groups of patients, the Scheffe technique for multiple group comparisons was used. Normal values were taken from the literature.[10,12,24,25,29,31]

Results

The three groups of patients had similar ages, weights, body surface areas, and burn sizes, and were studied at similar times following their injury (Table 1). The systemic responses to injury were comparable in all three groups, as reflected by similar rectal temperatures, pulse rates, blood pressure, cardiac indices, and total body oxygen consumption (Table 2). Because of the extensive injuries, cardiac output and oxygen consumption approached near maximal levels. Arterial concentrations of oxygen, glucose, lactate, and pyruvate were not significantly different among groups (Table 3). The mean arterial–hepatic vein oxygen content differences ($A\text{-}HV_{O_2}$) were 4.6 and 4.1 ml/dl in the unin-

* This technique[28] was selected over the more common constant infusion method because, in preliminary studies, steady state arterial ICG concentrations could not be achieved in four of six patients using the high-dose infusion rate suggested in the literature.[15] When lower doses were used, including those recommended for patients with cirrhosis,[27] completely unpredictable results were obtained. The bolus clearance technique also provided another advantage, since a marked reduction in the hepatic venous extraction with constant infusion signaled the development of back diffusion of the dye from the hepatocyte.[21] In these patients, however, back diffusion did not occur in the first 12–15 minutes postinjection.

¶ Lexington Instrument Corporation, Dallas, TX.

Gilford Instrument Laboratories, Inc., Oberlin, OH.

TABLE 2. *Systemic Responses (Mean ± SEM)*

Systemic Responses	Noninfected Burn Patients	Bacteremic Burn Patients	Bacteremic Burn Patients With Complications
Rectal Temperature (°C)	38.5 ± 0.3	38.6 ± 0.2	38.0 ± 0.5
Pulse (beats/min)	125 ± 5	115 ± 5	124 ± 7
Blood Pressure (mmHg)	132 ± 4 / 70 ± 4	141 ± 6 / 77 ± 3	138 ± 10 / 68 ± 4
Cardiac Index (L/min·m²)	8.17 ± 0.33	8.79 ± 0.41	7.67 ± 0.72
Oxygen Consumption (ml/min·m²)	228 ± 9	238 ± 8	244 ± 12

fected burn patients and those with bacteremia, similar to the range of 4–5 ml/dl reported in normals.[25] However, the bacteremic patients with complications had an expanded $A-HV_{O_2}$ difference of 6.7 ml/dl, significantly greater than the bacteremic patients. The arterial-hepatic vein gradient for glucose, in all three groups was similar to the 0.4–0.5 mM/L (8–10 mg/dl) reported in normal postabsorptive man,[24] although the arterial–hepatic vein concentration difference for lactate and pyruvate appeared increased when compared with normals. The arterial–hepatic vein alanine difference in the critically ill burn patients with complications was sharply reduced when compared to the bacteremic group.

The proportionality constants for green dye disappearance in the noninfected patients and in the bacteremic group were in the high normal range. This value was significantly decreased in those individuals with complications (Table 4). No alterations in indocyanine green dye extraction were noted among groups. Estimated splanchnic blood flow ranged between 1–2 liters/min·m², elevated above the normal values of 0.63–0.85 L/min·m². Splanchnic blood flow accounted for 15–20% of cardiac index, a finding similar to previous reports in burn patients.[15] Splanchnic oxygen consumption was twice normal in all three patients groups, with the splanchnic bed accounting for approximately 25–30% of the total oxygen consumed. No differences in splanchnic oxygen consumption were observed among patient groups.

The basal rate of splanchnic glucose output was approximately 50% above normal in the noninfected burn patients, and increased significantly above this level in the bacteremic burn patients (Table 4). However, glucose production was significantly less in the bacteremic patients with complications when compared with the other two patient groups; the rate of glucose output in the patients with complications was comparable to rates reported for normal postabsorptive subjects.

All burn patients demonstrated splanchnic uptake of lactate and pyruvate greater than rates reported for normals, but there were no differences between patient groups in arterial concentrations, per cent extraction, or hepatic uptake of these three-carbon glucose precursors. Assuming complete hepatic conversion of lactate and pyruvate to glucose in the injured subjects, these two substrates accounted for 30–50% of the glucose produced by the liver.

Marked differences were noted between groups with respect to the splanchnic exchange of amino acids. Of the 17 amino acids studied, consistently positive

TABLE 3. *Blood Concentration (Mean ± SEM)*

	Normal	Noninfected Burn Patients	Bacteremic Burn Patients	Bacteremic Burn Patients With Complications
Arterial Oxygen, ml/100 ml	15–18	14.1 ± 0.7	13.8 ± 0.7	14.0 ± 0.8
$A-HV_{O_2}$,* ml/100 ml	4–5	4.6 ± 0.5	4.1 ± 0.5	6.7 ± 1.0†
Arterial Glucose Concentration, mM/L	4.0–5.0	5.56 ± 0.22	7.11 ± 1.28	6.28 ± 0.56
A-HV Glucose, mM/L	−0.4–−0.5	−0.44 ± 0.05	−0.50 ± 0.05	−0.33 ± 0.05
Arterial Lactate Concentration, mM/L	0.5–0.7	1.022 ± 0.089	1.444 ± 0.256	1.533 ± 0.389
A-HV Lactate, mM/L	0.18–0.24	0.244 ± 0.044	0.278 ± 0.078	0.211 ± 0.067
Arterial Pyruvate Concentration, mM/L	0.06–0.07	0.090 ± 0.006	0.106 ± 0.008	0.118 ± 0.017
A-HV Pyruvate, mM/L	0.010–0.020	0.012 ± 0.005	0.011 ± 0.004	0.012 ± 0.005
Arterial Alanine Concentration, mM/L	0.250–0.400	0.345 ± 0.051	0.376 ± 0.062	0.170 ± 0.021
A-HV Alanine, mM/L	0.080–0.100	0.119 ± 0.028	0.196 ± 0.036	0.058 ± 0.020†

* A-HV: arterial-hepatic vein concentration.

† Bacteremic burn patients versus bacteremic burn patients with complications, $p < 0.05$.

TABLE 4. *Splanchnic Blood Flow and Rates of Substrate Exchange (Range or Mean ± SEM)*

	Normal	Noninfected Burn Patients	Bacteremic Burn Patients	Bacteremic Burn Patients With Complications
ICG and ESBF				
k/min	0.2–0.3	0.328 ± 0.027	0.273 ± 0.030	0.141 ± 0.021†
Indocyanine green dye per cent extraction	75–90	67 ± 4	50 ± 5	46 ± 8
Blood volume, ml/kg	70–80	82.4 ± 4.8	81.9 ± 6.3	104.8 ± 14.1
Estimated splanchnic blood flow, L/min·m²	0.63–0.85	1.54 ± 0.12	1.74 ± 0.17	1.19 ± 0.18
Splanchnic blood flow as a per cent of cardiac index	22–28	19.1 ± 1.8	20.1 ± 2.1	16.1 ± 2.5
Hematocrit per cent	39–46	34 ± 1	33 ± 1	33 ± 1
Splanchnic Exchange				
Splanchnic VO_2, ml/min·m²	34–40	68 ± 4	66 ± 5	73 ± 3
Splanchnic VO_2 as a per cent of total VO_2	20–25	29.8 ± 1.5	27.8 ± 2.2	30.3 ± 1.5
Glucose production, mM/min·m²	0.35–0.45	0.635 ± 0.035	0.835 ± 0.054†	0.362 ± 0.060†‡
Lactate uptake, mM/min·m²	0.13–0.16	0.377 ± 0.077	0.431 ± 0.107	0.268 ± 0.108
Per cent of glucose from lactate	20–24	30.5 ± 6.7	28.8 ± 7.4	45.5 ± 21.9
Pyruvate uptake, mM/min·m²	0.005–0.010	0.019 ± 0.008	0.018 ± 0.007	0.011 ± 0.004
Per cent glucose from pyruvate	1–3	1.52 ± 0.66	1.20 ± 0.44	1.32 ± 0.40
Alanine uptake, mM/min·m²	0.030–0.045	0.124 ± 0.031	0.213 ± 0.040	0.042 ± 11‡
Per cent of glucose from alanine	5–9	9.2 ± 2.3	13.2 ± 2.0	6.3 ± 1.5

* Noninfected burn patients versus bacteremic burn patients, $p < 0.05$.

† Noninfected burn patients versus bacteremic burn patients with complications, $p < 0.05$.

‡ Bacteremic burn patients versus bacteremic burn patients with complications, $p < 0.05$.

arterial–hepatic venous concentration differences (A–HV), indicating net uptake, were demonstrated in both the noninfected and bacteremic burn patients but not those patients with complications (Table 5). Gluconeogenic precursors predominated as the amino acids taken up by the liver. In the noninfected and bacteremic burn patients these included alanine, glycine, and tyrosine. A significant uptake of threonine and methionine was also observed in the noninfected burn patients and serine, proline, isoleucine, phenylalanine, and lysine were taken up by the bacteremic burn patients.

An increased splanchnic exchange of amino acids occurred in the noninfected burn patient when compared to hepatic amino acid uptake in postabsorptive normals. Alanine, which quantitatively is a major nitrogen transport compound from skeletal muscle to liver and provides a three-carbon skeleton as a glucose precursor, was taken up at an average of 124 μM/min·m² in the noninfected burn patients, rates three to four times those reported for postabsorptive normals (Tables 4 and 5). Since arterial concentrations of alanine in this group were within the normal range and the per cent amino acid extracted was comparable to levels reported in normals (approximately 36%[29]), the mechanism for this augmented alanine uptake was dependent on the increased delivery of the amino acids to the liver via the elevated splanchnic blood flow.

In the bacteremic patients, splanchnic uptake of amino acids increased markedly when compared with the noninfected burn patients. The total amino acid nitrogen taken up by the liver in the bacteremic burn patients averaged 131 ± 24 μM nitrogen/min·m², two to three times the uptake observed in the noninfected burn subjects (48.1 ± 10, $p < 0.01$). Since the arterial concentrations of the amino acids were similar in the two groups and blood flow was comparable, the augmented splanchnic amino acid uptake observed in the bacteremic patients was solely a consequence of increased fractional extraction by the splanchnic bed. The average per cent extraction for all the 17 amino acids studied was 26 ± 6% for the bacteremic burn patients, significantly greater than the 8 ± 6% ($p < 0.05$) in the noninfected burn group.

In the bacteremic burn patients with complications, the uptake of amino acids was reduced. Alanine exchange, for example, was significantly decreased in these individuals when compared to the bacteremic subjects. In most instances, the plasma amino acid arterial concentrations were less in the complicated bacteremic burn patients than in the other two groups, and the average extraction for all amino acids was only 3 ± 3%.

Renal arterial–venous differences demonstrated a widened $A-RV_{O_2}$ in the noninfected burn patients when compared to the bacteremic patients (Table 6). The kidney consistently consumed glucose in all patients studied. Renal vein catheterization was performed in only two individuals with bacteremia with complications. In these patients, the extraction of oxygen and

glucose was similar to those values observed in the bacteremic group.

Discussion

This current investigation provides direct evidence of altered glucogenesis which occurs following major injury. In the noninfected burn patients, rates of glucose production were one and one-half times greater than values reported in normal postabsorptive subjects. While the normal individual produces approximately 200 g of glucose/day, the thermally injured, noninfected patient releases approximately 320 g of glucose/day. This measurement of increased net splanchnic glucose production is consistent with data derived from tracer studies which suggest increased glucogenesis following injury.[18] This increased rate of glucose production is even more striking in face of the slightly negative calorie balance sustained by all patients during the time following injury and the fact that hepatic glycogen stores were probably partially depleted. Comparable studies in control individuals with some degree of caloric re-

TABLE 5. *Arterial Concentrations (A), Arterial-Hepatic Venous Differences (A-HV), Per Cent Hepatic Extraction, and Hepatic Exchange of Amino Acids (Mean ± SEM)*

	Noninfected Burn Patients				Bacteremic Burn Patients				Bacteremic Burn Patients with Complications			
	A, μM/L	A-HV, μM/L	% Extr.	Hepatic Exchange, μM/min·m²	A, μM/L	A-HV, μM/L	% Extr.	Hepatic Exchange, μM/min·m²	A, μM/L	A-HV, μM/L	% Extr.	Hepatic Exchange, μM/min·m²
Taurine	45 ± 15	−7 ± 6	−47 ± 35	−7.3 ± 5.3	63 ± 21	1 ± 6	30 ± 43	0.9 ± 6.0	44 ± 30	10 ± 12	57 ± 41	5.6 ± 7.2
Threonine	126 ± 17	50 ± 12*	36 ± 7	48.8 ± 10.6	115 ± 23	54 ± 23	37 ± 12	57.5 ± 28.1	95 ± 16	35 ± 11	37 ± 10	27.6 ± 8.7
Serine	136 ± 29	10 ± 18	−53 ± 65	12.8 ± 17.5	194 ± 31	88 ± 16*	47 ± 5	93.8 ± 13.1†	79 ± 18‡	26 ± 14	22 ± 15‡	18.7 ± 10.8‡
Proline	239 ± 53	14 ± 35	18 ± 21	9.5 ± 37.5	175 ± 36	69 ± 17*†	45 ± 11†	68.9 ± 12.3	29 ± 29‡	−12 ± 9	−3 ± 3	−1.6 ± 1.6
Glycine	269 ± 46	71 ± 33*	25 ± 7	66.5 ± 26.4	318 ± 41	128 ± 48*	38 ± 12	138 ± 61	158 ± 47	35 ± 35	−12 ± 43	29.7 ± 23.3
Alanine	345 ± 51	119 ± 28*	34 ± 5	124 ± 31	376 ± 63	196 ± 36*	53 ± 4	213 ± 40	170 ± 21	58 ± 20	33 ± 10‡	42.0 ± 11‡
Valine	143 ± 40	−12 ± 17	−3 ± 11	−17.9 ± 19.7	213 ± 28	31 ± 43	14 ± 16	65 ± 50	167 ± 27	38 ± 52	5 ± 35	34.0 ± 42
Cystine	23 ± 2	4 ± 3	27 ± 18	5.4 ± 3.8	41 ± 16	21 ± 20	−18 ± 43	18.0 ± 18.6	48 ± 14	27 ± 6	66 ± 16	24.2 ± 8.3
Methionine	27 ± 3	10 ± 2*	38 ± 9	9.8 ± 2.2	37 ± 9	15 ± 8	22 ± 15	15.6 ± 10.0	99 ± 61	77 ± 64	43 ± 16	85.2 ± 78
Isoleucine	81 ± 7	3 ± 8	1 ± 12	5.0 ± 6.4	85 ± 16	34 ± 12*	36 ± 10	38.3 ± 15.2	43 ± 12	4 ± 6	4 ± 21	5.2 ± 5.8
Leucine	136 ± 16	2 ± 13	0 ± 11	2.6 ± 10.8	102 ± 20	41 ± 17	30 ± 10	50.0 ± 24.1	96 ± 13	5 ± 25	−8 ± 26	8.8 ± 18.8
Tyrosine	70 ± 9	18 ± 6*	22 ± 10	19.3 ± 6.4	66 ± 15	32 ± 10*	31 ± 19	35.7 ± 11.9	62 ± 19	−6 ± 11	−20 ± 38	4.8 ± 11.8
Phenylalanine	138 ± 19	26 ± 20	12 ± 16	32.2 ± 22.1	142 ± 21	63 ± 17*	40 ± 9	67.9 ± 21.1	94 ± 35	27 ± 11	26 ± 9	21.5 ± 9.8
Ornithine	112 ± 34	21 ± 25	10 ± 13	28.9 ± 32.6	77 ± 34	−4 ± 22	26 ± 13	12.4 ± 10.3	77 ± 33	18 ± 51	−73 ± 88	35.2 ± 53.4
Lysine	160 ± 17	32 ± 17	19 ± 10	35.3 ± 19.2	217 ± 48	109 ± 34*	47 ± 8	119.3 ± 46.9	131 ± 25	52 ± 38	15 ± 37	40.6 ± 35.1
Histidine	68 ± 9	2 ± 12	3 ± 16	6.7 ± 14	76 ± 15	10 ± 16	0 ± 62	9.3 ± 16.6	53 ± 9	9 ± 11	13 ± 24	11.8 ± 10.7
Arginine	69 ± 11	−11 ± 16	9 ± 22	−12.2 ± 17.4	28 ± 11	−1 ± 4	−35 ± 33	−0.3 ± 5.2	30 ± 12	−9 ± 23	−149 ± 93	1.0 ± 23.0

* Arterial and hepatic venous concentrations significantly different by paired *t*-test, $p < 0.05$.

† Noninfected burn patients versus bacteremic burn patients, $p < 0.05$.

‡ Bacteremic burn patients versus bacteremic burn patients with complications, $p < 0.05$.

striction are not available, but the study of Garber et al. demonstrated that with only three days of starvation there is a marked fall in hepatic glucose production, to approximately half the quantity of glucose produced in postabsorptive man.[13] Finally, renal catheterization data demonstrated that the kidney does not participate in the increased glucose production following injury, and that this function is solely the responsibility of the liver.

In addition to the increase in glucose produced, these data provide evidence of altered gluconeogenesis following injury. First, the net splanchnic uptake of lactate and pyruvate appear greater than observed in control subjects,[29] suggesting increased Cori cycle activity following burn injury. This observation agrees well with the finding of increased glucose uptake and lactate release across injured, but not uninjured, extremities.[31] Approximately 80% of the glucose consumed by the burn wound is converted to lactate, and previous estimates of peripheral lactate production are quite comparable to these measurements of splanchnic lactate uptake.[30,31]

Secondly, the enhanced uptake of alanine and other glucogenic amino acids in the noninfected burn patients is further evidence of an accelerated rate of hepatic gluconeogenesis following injury. Because plasma and not whole blood amino acids were measured the total splanchnic uptake of amino acids is probably underestimated.[2] However, Chiasson and associates demonstrated that 90–95% of the alanine exchanged across the hepatic bed was transported in serum, and thus alanine can be followed as an index of skeletal muscle–hepatic exchange of amino acids.[8] Alanine exchange in the noninfected burn patients was three to four times the splanchnic uptake observed in normal man.[11] Moreover, splanchnic alanine exchange rates of 200–220 μM/min in the noninfected burn patients compare favorably with the estimates of peripheral alanine release previously reported.[4] Alanine generally accounts for 30–50% of the new glucose derived from amino acids,[11] but in these injured patients 100% conversion of this gluconeogenic amino acid to new glucose may not occur. This is based on the observation of Long and associates, who administered C^{14}-alanine to critically ill patients and found that as much as 32% of the tagged carbon rapidly appeared as expired CO_2.[19] However, assuming complete conversion of glucogenic amino acids to new glucose, as much as 20–30% of the glucose produced in the noninfected burn patients could be derived from th carbon skeletons of these amino acids (Fig. 1). This value compares favorably with theoretical calculations of glucose derived from amino acids based on the quantity of nitrogen excreted in the urine.** In contrast to postabsorptive normals in whom only 20–25% of hepatic glucose output can be accounted for by gluconeogenesis,[29] noninfected burn patients could derive approximately half of their glucose from three carbon precursors.

TABLE 6. *The Arterial-Renal Vein Differences* for Oxygen, Glucose and Lactate (Mean ± SEM)*

	Normal	Non-Infected† Burn Patients	Bacteremic‡ Burn Patients
Oxygen (ml/100 ml)	1.6–1.8	2.41 ± 0.14	0.92 ± 0.18§
Glucose (mM/L)	0–0.056	0.222 ± 0.056	0.056 ± 0.056§
Lactate (mM/L)	−0–−0.001	−0.044 ± 0.008	0.066 ± 0.018

* Only two of the complicated bacteremic burn patients underwent renal vein catheterization. The A–RV difference results were similar to those reported for the bacteremic patients. Renal blood flow, however, was decreased and averaged 0.447 ± 0.048 L/min·m².

† Renal blood flow measured in six subjects averaged 0.693 ± 0.074 L/min·m². Normal = 0.552 ± 0.037.

‡ Renal blood flow measured in three subjects averaged 1.970 ± 0.380 L/min·m².

§ $p < 0.05$ when compared with noninfected burn patients.

Finally, it is important to note that the increased hepatic uptake of glucose precursors closely matched the peripheral release of these substances, and thus serum substrate concentrations were maintained at near normal levels. Because the per cent extractions of lactate, pyruvate and gluconeogenic amino acids from the blood in the noninfected burn patients were comparable to normal values, the increased splanchnic uptake of these substances following injury was the consequence of greater substrate delivery provided by the increased splanchnic blood flow.

With the onset of bacteremia, hepatic glucose production increased. While the exchange of lactate and pyruvate was not altered when compared to the noninfected burn patient, the uptake of amino acids was significantly increased in the bacteremic patients. The increased hepatic utilization of these glucose precursors with bacteremia could be a consequence of either greater substrate availability or augmented hepatic extraction of circulating substrate. Because blood flow and substrate concentrations did not change between these two groups, there is little evidence of increased amino acid availability in the bacteremic patient.

** It has been suggested that 4.66 grams of nitrogen from catabolized protein should yield approximately 16 grams of glucose.[26] Since these patients excrete 20–30 grams N/day, approximately 80 grams of glucose are theoretically derived from nitrogen containing compounds each day. Thus approximately 25% of the total 320 grams glucose/day produced in the non-infected burn patient can be accounted for arising from amino acids.

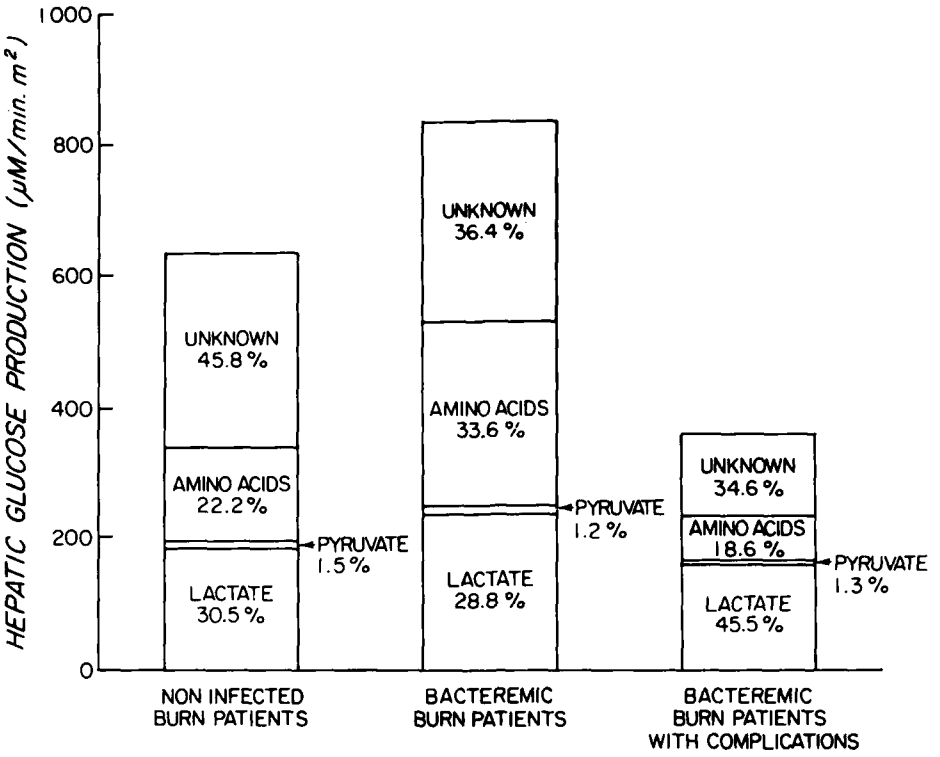

FIG. 1. Hepatic glucose production in the three groups of patients is significantly different among groups. The amino acid calculation is based on the contribution of the glucogenic amino acids which are known to serve as glucose precursors in normal postabsorptive man (Ala, Gly, Thr, Ser, Tyr, Phe). Lactate uptake was similar among the three groups but amino acid uptake was significantly different among the groups.

However, there was increased extraction of amino acids in the bacteremic patients when compared with the noninfected burn subjects. These data suggest that the augmented hepatic uptake of gluconeogenic amino acids is the consequence of altered intrahepatic metabolism as a consequence of sepsis, as opposed to an increased availability of precursor substrate. The fact that serum concentrations were maintained at levels comparable to those observed in the noninfected subjects, support the thesis that this increased hepatic amino acid uptake was matched by augmented peripheral release. Finally, all of these alterations occurred without changes in regional blood flow or oxygen utilization. The usual response to infection in previously healthy individuals is to increase oxygen consumption, cardiac output, and splanchnic blood flow,[1,7,16] but these alterations were not observed in the infected burn patients when compared with the noninfected burn subjects, presumably because of the near maximal total body metabolic and circulatory responses to burn injury attained before the onset of infection.

In contrast to the first two groups of patients, the septic patients with complications demonstrated diminished hepatic glucose production, reduced amino acid exchange, but comparable lactate uptake. It is well known that alterations in hepatic production and tissue uptake of glucose occur in association with severe infection.[6,37] The most dramatic symptom complex observed is hypoglycemia in the newborn associated with gram negative sepsis.[39] While animal studies suggest that severe infection impairs hepatic glucose production,[17,20] increased clearance (tissue uptake) of glucose has also recently been implicated.[38] It has been suggested that endotoxin blocks hepatic glucose production,[20] although the precise role of this and other bacterial products in the metabolic response to infection is unknown. However, the commonly used liver function tests did not reflect these severe functional abnormalities, characterized by a reduced glucose production and a diminished amino acid exchange, seen in the complicated bacteremic burn patients. In contrast however, the clearance of indocyanine green dye was abnormal. This and previous work suggests that this test may be used as a measure of hepatic dysfunction in critically ill patients.[21,22] If hepatic amino acid uptake was impaired and skeletal muscle amino acid release continued at previous rates, the arterial serum amino acid concentrations would rise. Because low, not elevated, amino acid levels were observed in the septic patients with complications, the data suggests that mechanisms which regulate skeletal muscle amino acid release are also altered. Although hormone concentrations were not obtained in these patients, previous investigations in similar individuals have demonstrated an excess, not a

lack, of counterregulatory hormones which stimulate gluconeogenesis in burn patients with sepsis and complications.[32-34] Because hypoaminoacidemia, diminished hepatic amino acid extraction and reduced glucose production can be reproduced by administering insulin (and glucose) to normals,[12] it is important to note that hyperinsulinemia has not been previously found in similar patients.[32-34] Thus, the exact mechanisms for this altered glucose output in the severely ill patients are not precisely known, but the metabolic impact appears to affect both the liver and skeletal muscle.

Blood oxygen and substrate concentrations are measured with a high degree of precision and accuracy. Splanchnic blood flow, however, is not as reliable a measurement.[28] The crux of the evidence demonstrating altered net splanchnic glucose production in infected, critically ill subjects rests on the calculation of hepatic glucose production rate which requires an estimate of splanchnic blood flow. This flow measurement is based on the hepatic uptake of indocyanine green dye and the kinetics of this inert dye are disturbed following infection and endotoxemia.[21,22] Thus, as patients develop complications, indocyanine green dye uptake decreases and these alterations may add to variability of the splanchnic blood flow measurement. However, there are several lines of evidence that support the validity of these regional flow measurements. Although burn size, time of study, and other patient characteristics are not identical to the patients studied by Gump et al., the per cent of cardiac output directed to the splanchnic bed in this study is comparable to previous measurements in burn patients.[15] The splanchnic bed accounts for a large portion of the oxygen consumed by the body and in nonexercising patients this quantity is roughly proportional to the total body oxygen consumption. In this study, the total body oxygen consumption was similar in the patient groups, and splanchnic oxygen consumption (calculated using the blood flow measurement) was also comparable. Moreover, in the infected patients with complications, as the splanchnic blood flow fell, the $A-HV_{O_2}$ correspondingly increased. Studies in these and comparable patients have quantitated blood flow to the extremities[31] and skeletal muscle.[5] These flow studies combined with the present measurements account for most, if not all, of the increased cardiac output following burn injury. Thus, the splanchnic blood flow and regional oxygen consumption measurements presented in this report together with similar studies across other regional beds, adequately account for the cardiac output and the total body oxygen consumption which occurs in the severely burned patient.

In summary, these studies indicate that: 1) hepatic glucose production increases following major injury; 2) bacteremia in severely injured patients further augments gluconeogenesis by the increased hepatic uptake of amino acids; 3) with septic complications, hepatic glucose production and amino acid uptake decreases and; 4) these changes occur without alterations in splanchnic blood flow, oxygen utilization or lactate uptake.

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APPENDIX

Case 1. 23-Year-Old Man With A 61% Total Body Surface Burn Studied Throughout His Hospital Course

Postburn day studied	15	64	127
Clinical status	*S. aureus* bacteremia	partially grafted no infection	convalescing before hospital discharge
Per cent open wound	61	20	0
Rectal temperature (°C)	38.5	37.7	37.0
Pulse rate (beats/min)	132	128	88
Weight (kg)	50.5	46.4	46.0
Body surface area (m^2)	1.60	1.53	1.51
Cardiac output (L/min)	12.40	11.19	8.67
Oxygen consumption (ml/min)	400	304	196
Splanchnic blood flow (L/min)	3.120	2.238	1.300
Per cent C.O. to splanchnic bed	25.2	20.0	15.0
A–HV_{O_2} (ml/100 ml)	3.14	3.48	5.54
Splanchnic oxygen consumption (ml/min)	98	78	72
Per cent O_2 to splanchnic bed	24.5	25.7	36.7
Hepatic glucose production (M/day)	2.49	1.61	1.04

Comments

This patient was first studied after successful resuscitation, followed by three days of positive blood cultures for *Staphylococcus aureus*. On the fifteenth day postburn, blood cultures were still positive for this organism, and the patient exhibited a hyperdynamic circulation with a large portion of his cardiac output and oxygen consumption being accounted for by flow to the splanchnic bed. Hepatic glucose production at the time of the infection exceeded twice normal levels. Antibiotic therapy cleared the Staphylococcal infection and a large portion of his second degree burn then healed. On the sixty-fourth postburn day he was studied again; cardiac output, splanchnic blood flow, and total body and regional oxygen consumption were still elevated above normal, but to a lesser degree. Hepatic glucose production remained elevated but had also decreased from the previous study period. On the 127th day postinjury, the patient was convalescing after burn wound closure. The patient's cardiac output was still abnormally high, presumably because of the increased perfusion still present in the healed wounds. However, oxygen consumption had returned to normal. In spite of the normal total oxygen consumption, the splanchnic bed accounted for a greater than normal percentage of the oxygen consumed. This may be due to the tremendous metabolic burden that the liver had sustained, or may be related to the fact that this man had undergone marked loss of muscle mass which resulted in the reduced carcass oxygen consumption. Hepatic glucose production returned to normal values at the time of the last study. Finally, in additional studies, it was noted that his patient has undergone renal hypertrophy. Blood flow to his kidneys measured during this period of convalescence was also markedly increased.

Case 2. Blood Flow Inappropriately Elevated For Oxygen Extraction In This 24-Year-Old Man With 47% Total Body Surface Burns and Gram Negative Bacteremia

Postburn day studied	11	18	53
Clinical status	On ventilator + blood cultures for *P. aeruginosa*	On ventilator. Clinical signs of infection resolved. Blood cultures show no growth	Off ventilator. Donor sites on legs.
Rectal temperature (°C)	39.2	38.3	38.7
Pulse rate (beats/min)	128	120	112
Weight (kg)	71.2	70.4	64.1
Body surface area (m^2)	1.87	1.86	1.76
Cardiac output (L/min)	18.15	14.17	13.70
Oxygen consumption (ml/min)	455	536	334
Central A-V O_2 difference (ml/100 ml)	2.51	3.78	2.44
Splanchnic blood flow (L/min)	4.690	4.146	3.358
Per cent C.O. to splanchnic bed	25.8	29.3	24.4
Arterial–hepatic vein O_2 difference (ml/100 ml)	1.9	3.36	3.0
Splanchnic oxygen consumption (ml/min)	89	139	100
Per cent O_2 to splanchnic bed	19.6	25.9	29.9
Arterial–renal vein O_2 difference (ml/100 ml)	0.58	1.78	2.3
Arterial–femoral vein O_2 difference (ml/100 ml)	1.9	5.36	4.2

Comments

Cardiac output increases with infection, and it has been suggested that some of the increase in circulation may be due to generalized vasodilatation with high flow through regional beds and diminished extraction of oxygen. This was not characteristically seen in the burned patients studied. However, the exception to the rule appears in this 24-year-old man who had positive bloodstream cultures for *P. aeruginosia* due to severe pneumonia. On the eleventh postburn day, he was studied and found to have a high cardiac output and a high splanchnic blood flow. Note that the arterial–venous oxygen differences across the splanchnic bed, kidney, and leg and lungs are markedly narrow. Use of appropriate antibiotics and vigorous respiratory toilet resulted in the clearing of the pneumonia. His cardiac output diminished while his oxygen consumption increased. Oxygen extraction across the regional beds returned toward normal. The data from the fifty-third postburn day were obtained when some burn wounds remained open, and donor sites were present on the patient's legs.

Case 3. Effect of Body Heating in a 25-Year-Old Male With a 56% Total Body Surface Burn Who Later Developed Burn Wound Sepsis

Postburn day	8		20	29
Clinical status	hypothermia hypovolemia	following environmental heating	invasive Pseudomonas burn wound infection in left leg	on ventilator with bacteremia and renal failure
Rectal temperature (°C)	36.5	39.1	37.6	37.9
Pulse rate (beats/min)	100	120	112	120
Weight (kg)	80.2		80.1	79.8
Body surface area (m^2)	1.99		1.99	1.98
Cardiac output (L/min)	15.57	17.55	21.3	18.67
Oxygen consumption (ml/min)	418	429	436	470
Central A-V O_2 difference (ml/100 ml)	2.68	2.44	2.05	2.52
Splanchnic blood flow (L/min)	1.623	1.546	2.884	1.808
Per cent C.O. to splanchnic bed	10.4	8.8	13.5	9.7
A–hepatic vein O_2 (ml/100 ml)	9.0	9.7	4.82	7.8
Splanchnic oxygen consumption (ml/min)	146	150	139	141
Per cent O_2 to splanchnic bed	34.9	34.9	31.9	30.0
Hepatic glucose production (M/day)	1.30	—	2.54	1.16
A–renal vein O_2 (ml/min)	4.8	—	1.13	0.4
Renal blood flow (L/min)	—	—	0.996	0.783
Renal oxygen consumption (ml/min)	—	—	11.2	3.0
Per cent O_2 to kidney	—	—	2.6	0.6
A–femoral vein O_2 (ml/100 ml)	3.2	1.4	0.63	2.2

Comments

On the eighth postburn day this patient was hypothermic and hypovolemic by blood volume determination. Following initial investigations, the patient remained in the environmental chamber and was heated so that his core temperature rose from 36.5 to 39.1 C. The effect of environmental heating alone on this man's circulatory status is shown. Cardiac output and splanchnic blood flow increased slightly and A-V difference across the leg narrowed, suggesting peripheral vasodilatation. On the twentieth postburn day, invasive Pseudomonas infection developed in the burn wound on the patient's left leg. This invasive infection was associated with a tremendous increase in cardiac output and hepatic and renal blood flow. The narrow A-V O_2 difference across the kidney (normal 1.5–1.8 ml/dl) was associated with diminished renal oxygen consumption. The narrow arterial-femoral vein O_2 difference which was obtained from the leg with the infection suggests a marked increase in flow to this extremity. This finding is similar to results from animal experiments: sepsis in a leg results in a narrow A-V

difference and increased leg blood flow.†† In spite of operative debridement and vigorous antibiotic care, the patient continued to have bacteremia and required ventilatory support. His renal function continued to deteriorate. The study obtained on the twenty-ninth postburn day still demonstrates an increased cardiac output and a large splanchnic bed blood flow. Renal blood flow is now markedly diminished and renal oxygen consumption further reduced. Hepatic glucose production has fallen from the elevated levels seen in noninfected burn patients, and this reduction in glucose production was a characteristic finding in patients studied with multiorgan system failure.

†† Hermreck AS, Thal AP. Mechanisms for the high circulatory requirements in sepsis and septic shock. Ann Surg 1969; 170:677.

Discussion

Dr. Josef E. Fischer (Cincinnati, Ohio): This is another one of those elegant studies that Dr. Wilmore and Dr. Pruitt and their coworkers have been carrying out, enlarging our understanding of organ failure, especially in burn patients, and as applied to all patients in overwhelming sepsis, which is being identified as the critical area in the care of surgical patients, and the problem of sequential organ failure.

We have been interested in this area from a slightly different point of view. Two years ago, before this society, Dr. Freund and I suggested (slide) evidence that had impact on this area from the standpoint of amino acid metabolism, and which it is interesting to see in Dr. Wilmore's data today. In a first group of patients, we were able to predict from a single plasma amino acid pattern mortality. Nonsurvivors shown here had lower levels of branched-chain amino acids, lower alanine levels, higher aromatic amino acid levels and higher levels of sulfur-containing amino acids. Dr. Wilmore's complicated bacteremic patients, perhaps, were similar.

(slide) In 1979, Dr. Freund presented additional evidence in a larger group of patients, in which a single plasma amino acid sample was predictive of septic encephalopathy and mortality, with an 80–90% degree of accuracy in this group of 40 patients.

It is interesting, if one looks at the amino acids that are used in this discriminant function, that they are almost all the amino acids that the liver either metabolizes primarily or influences the concentration of which in the bloodstream.

(slide) This slide is interesting because it is not drawn about septic patients, but in another metabolic encephalopathy, liver failure. It was interesting to me to see that decreased energy production and altered amino acid patterns are a common mechanism of death both in sepsis and in overwhelming sequential organ failure, with liver destruction being, perhaps, one of the key factors, as well as cirrhosis.

Like many excellent papers, this paper raises many more questions than it answers, and some of the questions address the mechanism of death in these patients.

First, what is the mechanism by which liver failure occurs? We all seem to be picking up a change in the metabolism of this vital organ, ultimately resulting in decreased energy production and liver failure.

In the interpretation of the data in the manuscript, there is an appropriate note of caution concerning the methodology. The indocyanine green technique is difficult to carry out. It involves many assumptions concerning the uniformity of hepatic blood flow, especially when one is catheterizing a single hepatic vein. There is no assurance that in the six septic patients in which hepatic function was deteriorating there was uniformity of extraction or, in fact, that the methodology was applicable at all. In the manuscript this is dealt with appropriately. Unfortunately, I cannot suggest anything better. A lot of the data, and the interpretation of the data, particularly the extraction, really depend on the accuracy of hepatic blood flow.

My second question also involves the interpretation of data, and this is, perhaps, whether or not that unknown amount of glucose production might conceivably result from donation by the liver itself of amino acids ordinarily intended from structural protein, in which these amino acids are being contributed for gluconeogenesis, on a teleologic basis, perhaps, for glucose to keep the central nervous system alive. In fact, this is an insult from which the liver and the kidneys never recover, namely, the donation of their own important enzymatic and structural protein for gluconeogenesis. A black-box method, which I suspect this is, measuring amino acids in, amino acids out, probably would not pick this up, if, in fact, the liver itself were the nitrogen donor, instead of the periphery. I would like Dr. Wilmore's comments about that.

Third is the question of what finally happens when hepatic protein synthesis fails. Is there anything in the data in these studies suggesting that fatty acid oxidation, which is the normal supply of energy for hepatic protein synthesis, fails at the critical time when these patients convert from being bacteremic to being septic and bacteremic? Are there any data from the flux studies that suggest that this may be the situation?

Dr. George H. A. Clowes, Jr. (Boston, Massachusetts): Dr. Wilmore has shown us a number of important metabolic functions of the liver in man as they are affected by trauma and sepsis. His findings are somewhat difficult to interpret unless one remembers that a dramatic change in mobilization of amino acids and production of lactate occur in the posttraumatic or septic states when compared with normal fasting or starvation. In the latter proteolysis predominantly takes place in the viscera, while in sepsis the peripheral tissues, principally muscle, are the greatest source of amino acids transferred to the central tissues for gluconeogenesis, oxidation or synthesis of the proteins essential to survival. The proof of this is found in the experiments of Dr. Tom Ryan of our group, who demonstrated that in normal rats starved three days the fat almost disappeared and liver weight was below normal. By contrast, the septic animals with induced peritonitis had livers which contained considerably more protein than normal.

The point of this is that after injury or during infection the liver must clear the greater peripheral release of amino acids and lactate coming from the muscles. The liver really has only two methods for clearance. The first is deamination of amino acids for oxidation or glucogenesis. The second is synthesis of proteins or peptides of a wide variety. Both are energy-requiring processes, and it is a little surprising that Dr. Wilmore failed to find an increase of oxygen consumption in the sick patients. As Dr. Fischer stated, measurement of blood flow by dye clearance is variable under disease conditions, and calculation of oxygen uptake in the liver is at best difficult. For all of the conclusions relative to hepatic uptake and release of various substances, determination of flow is of major importance.

I wish Dr. Wilmore had given us the blood concentrations. These are a measure of pool size. Recently we have been looking at the peripheral production of amino acids and their clearance by central tissues. The clearance rate, or the proportion of the extracellular pool cleared per minute, gives a good indication of which patient is getting into trouble with liver failure. The clearances of amino

acids which really show the difference as to who is going to have trouble and who is not are the aromatics and the sulfurs, cystine and methionine, which also agrees with Dr. Fischer. I would like to hear from Dr. Wilmore about whether lactate as well as amino acids were accumulating in these patients.

DR. STANLEY M. LEVENSON (Bronx, New York): I'd like to ask Dr. Wilmore to speculate on the basis for some of the observations reported this morning: 1) Is the increased blood flow and increased oxygenation, demonstrated in all groups a reflection of more hepatocytes metabolizing at any given moment or an increase in the metabolic rate of hepatocytes per se? There is evidence, for example in terms of albumin synthesis, that at any one time probably only a third to a half of the hepatocytes are synthesizing and secreting albumin. That is, not every hepatocyte is functioning at any given time, at least in terms of the albumin synthesis. 2) Since there was no change in hepatic oxygen consumption, despite the very marked decrease (a factor of 2) in gluconeogenesis—and you will remember the diagram he showed indicating the heat expenditure associated with gluconeogenesis, what are the other oxygen consuming reactions which come into play as gluconeogenesis falls? 3) What is the signal for the changes he has observed? For example, at one level, what are the hormonal changes going on at this time, particularly as affecting the liver and other key organs which turn off gluconeogenesis?

In closing, as Fischer said, the data raise many questions. Drs. Wilmore and Pruitt and their colleagues realize, as we all do, that these studies are still at a descriptive level. We would like to hear their speculations as to what underlies what they have shown us this morning.

DR. JOHN M. KINNEY (New York, New York): One of the first things that was presented was the fact that glucose output from the liver is increased in proportion to the uptake of the precursors for glucose in noninfected patients. I think we might have expected that. However, it was striking that when bacteremia developed in these patients there was a sharp increase in the amino acid uptake.

Would Dr. Wilmore comment on whether the extra amino acid uptake could have been only for additional glucose synthesis?

At this time when a person becomes bacteremic, if they are not in shock, it would seem possible that the liver might be called upon to make extra acute-phase protein. I wonder if Dr. Wilmore has other evidence that this all went for glucose production, and, presumably, for an increase in urea output.

Another aspect of interest has to do with a change between the bacteremic patients who were not complicated and Dr. Wilmore's final group that had beginning organ failure. The liver has a dual responsibility toward peripheral tissues in terms of amino acid uptake. One is the constant effort to try to normalize circulating amino acid patterns; the other has to do with modifying amino acid uptake in terms of protein synthesis in other tissues. Would Dr. Wilmore comment on the blood levels of the substrates coming to the liver and of the glucose leaving the liver?

There has been a continuing controversy over what signals the liver to change its output of glucose. Is this because of an intrinsic metabolism of the liver itself, or is it because of a change in the substrates being brought to the liver? I wonder if Dr. Wilmore has made the calculations to see whether both of these are involved, or is it primarily liver failure, as suggested by Dr. Fischer.

Many of us have tended to think of the hypermetabolic surgical patient as embodying a sort of metabolic package; along with this increased energy expenditure is increased urea production, increased hepatic output of glucose, increased mobilization and oxidation of fat and so on. Dr. Wilmore has shown us in these patients with complications that there is a definite dissociation, one occurring without the presence of shock. There is a sharp reduction in glucose output, but the oxygen consumption is staying at the same high level.

I wonder if Dr. Wilmore would comment on what purpose this continued high oxygen consumption is serving presumably in the face of failing oxidative work in the liver and maybe other organs too.

DR. DOUGLAS W. WILMORE (Closing discussion): I would like to direct my answers to the discussants' questions in four general categories.

First, are comments regarding the measurement of splanchnic bloodflow. My associates and I examined the technique of measuring splanchnic blood flow by the constant infusion technique and by bolus injection of indocyanine green dye. We found that determination of blood flow based on the disappearance curve after the bolus injection of dye appeared preferable. However, the substrate data may be examined without the flow measurements; for each liter of blood passing through the liver, an amount of oxygen is consumed and a quantity of glucose is produced and amino acids extracted. There is no question that bacteremic patients with complications are extracting far more oxygen for the amount of glucose produced and at the same time extracting far less amino acids. However, when comparing splanchnic blood flow measurements with the results reported by others, our studies are quite similar. Moreover, measurements of muscle and extremity blood flow combined with these splanchnic studies account for most, if not all, of the distribution of the cardiac output. These facts all add additional credence to the blood flow measurements made in these critically ill patients. Moreover, with the narrow arteriovenous glucose difference across the splanchnic bed, hepatic blood flow would have to exceed well over 60% of the cardiac output in critically ill patients with complications in order to account for an increase in glucose production; proportion of visceral hyperemia simply does not occur in these patients. All these factors then aid data interpretation and support our conclusions concerning both blood flow and substrate influx.

The second point to discuss is the technique of measuring net flux of substrates across the liver. We are measuring substrate input and output across a regional bed and multiplying the arteriovenous difference by blood flow through that bed. This technique does not measure total production. Rather we need to combine these net measurements with isotopic turnover measurements to see if, as Dr. Fischer suggests, the liver in critically ill patients with complications may be consuming glucose at the same time it is releasing it. The same may occur with amino acids and therefore account for the narrow arteriovenous substrate difference across the splanchnic beds seen in the patients with sepsis and complications.

Are the amino acids taken up by the liver directed toward glucose production? The answer is clearly no. We have measured the arterial plasma concentrations of acute phase protein simultaneously in these same patients, and some of the results are shown on the table (all results in mg/dl, ±SEM).

	Normal Values	Non-infected Burn Patients	Bacteremic Burn Patients	Bacteremic Burn Patients with Complications
C-Reactive Protein	<1.2	25.0 ± 3.5	26.7 ± 3.5	14.1 ± 1.8
α_1 Acid Glycoprotein	55–140	5551 ± 89	1342 ± 85*	1175 ± 186†
Transferrin	200–400	186 ± 17	86 ± 7	114 ± 25

* $p < 0.01$ by Scheffe test, bacteremic versus noninfected burn patients.

† $p < 0.01$, bacteremic burn patients with complications versus noninfected burn patients.

These changes in plasma protein concentrations suggest that a significant portion of the peripherally released amino acids are directed for acute phase protein synthesis. This is particularly true in the case of the α_1 acid glycoprotein level, which increases markedly in infection. It is important to re-emphasize that with the onset of bacteremia, there is a marked increase in amino acid uptake by the liver. This occurs even though there is no concurrent alteration in hepatic oxygen consumption or splanchnic blood flow. As amino

acids are extracted in increased amounts, glucose production increases as does the α_1 acid glycoprotein level.

One other area that the discussants asked about was the relation between hepatic oxygen consumption and the metabolic work performed by the liver. It appears that free fatty acids are the primary oxidized fuel being used by the body. The energy provided for the synthesis of glucose and acute phase proteins is likewise most probably provided by free fatty acids. In the bacteremic patients with complications, oxygen consumption is maintained, yet glucose production falls. We cannot exclude the possibility that there is oxidative uncoupling in the liver of these individuals with complications, but likewise the energy may be diverted for other synthetic purposes or to support membrane pumps.

Amino acid concentrations in injured and bacteremic patients are generally near normal levels. The livers in the individuals with bacteremia increased amino acid uptake by increasing extraction; the percentage of amino acids extracted equalled approximately 8% in the noninfected burn patients, rose to 26% in the injured patients with bacteremia, and then fell to only 3% in the bacteremic patients with complications.

What is the signal that initiates this alteration in intrahepatic metabolism? Other studies suggest that glucagon, cortisol and catecholamines all stimulate these alterations. Moreover, the decreased glucose production and diminished extraction of amino acids observed in the bacteremic patients with complications can be duplicated in normal individuals by administering insulin. It should be noted that many investigators have suggested that severe sepsis mimics insulin administration: blood glucose falls, amino acid concentrations decrease, and amino acid extraction across the liver narrows. However, insulin level in these patients is rarely elevated, and the cause of these abnormalities appears related to the septicemia.

Dr. Levinson asks if we are simply observing more hepatocytes being perfused or are the individual hepatocytes becoming "hypermetabolic." The splanchnic arteriovenous difference for oxygen was normal in the traumatized patients, and extraction of substrate was likewise normal. The major physiologic alteration was the increase in regional blood flow. This evidence is compatible with the suggestion that the hepatocytes are extracting substrates at normal rates and supports the thesis that more hepatocytes are being used simply because of the increased perfusion and exposure to blood, rather than the discrete hepatocyte becoming markedly altered in its metabolic function.